ATLAS OF TUMOR PATHOLOGY

Third Series
Fascicle 13

TUMORS OF THE LOWER RESPIRATORY TRACT

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TUMORS OF THE LOWER RESPIRATORY TRACT

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CARCINOMA OF THE LUNG: OVERVIEW, INCIDENCE, ETIOLOGY, AND SCREENING

OVERVIEW

The common tumors generally included under the heading of carcinoma of the lung are squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and large cell carcinoma. These tumors share many clinical, etiologic, and demographic features. Bronchioloalveolar carcinoma is included as a subset of adenocarcinoma, although it has distinctive features of its own.

The incidence of the major subtypes of lung carcinoma from several large studies is shown in Table 7-1. Most recent series suggest that adenocarcinoma is now more frequent than squamous cell carcinoma (fig. 7-1) (4,12): in fact, adenocarcinoma represented 56 percent of the lung carcinomas seen at Johns Hopkins Hospital from 1984 to 1987 (7). Adenocarcinoma is the most frequent subtype seen in women. A relative decrease in the incidence of squamous cell carcinoma has accompanied the increased incidence of adenocarcinoma from the 1960s through the 1980s (1,3,6, 12,13). Although not as dramatic as the change

Table 7-1

FREQUENCY OF SUBTYPES OF LUNG CARCINOMA

Cell Type	Percent of Cases
A. Series prior to 1985 (21,139 cases)*	
Squamous cell carcinoma	37.7
Adenocarcinoma	24.9
(Bronchioloalveolar carcinoma: 2-2.8%)**	
Small cell carcinoma	18.7
Large cell carcinoma	18.7
B. SEER data 1983-1987 (59,260 cases)†	
Squamous cell carcinoma	30.0
Adenocarcinoma	32.2
(Bronchioloalveolar carcinoma: 0.7%)	
Small cell carcinoma	18.2
Large cell carcinoma	9.7
Other/unspecified	9.9

*From references 3,6,11,13 primarily reflecting data from prior to 1985.
**From references 10,13.
†From reference 12.

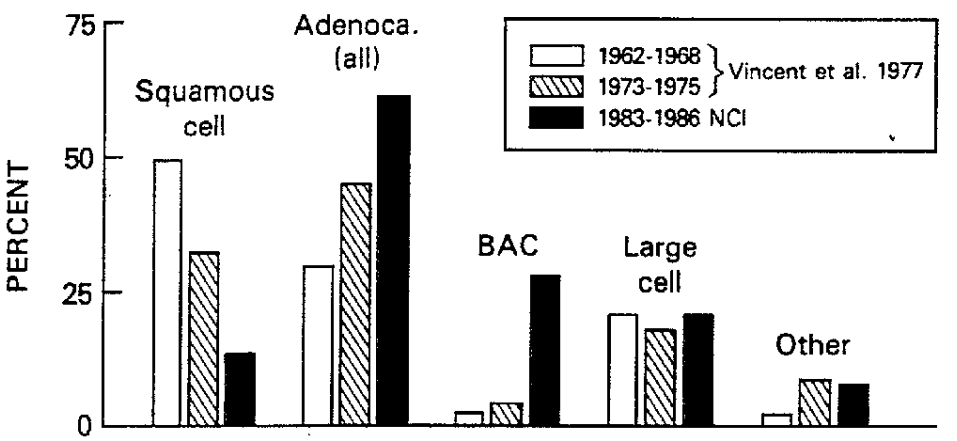


Figure 7-1
INCIDENCE OF LUNG CARCINOMA

The changing incidence of squamous cell carcinoma, adenocarcinoma, bronchioloalveolar carcinoma, and large cell carcinoma is shown for three time periods between 1962 and 1986. The period from 1983 to 1986 is represented by 100 consecutive cases seen by the National Cancer Institute, whereas data for the two earlier periods are from the literature. (Fig. 1 from Gazdar AF, Linnoila RI. The pathology of lung cancer—changing concepts and newer diagnostic techniques. Semin Oncol 1988;15:215–25.)

in the incidence of adenocarcinoma, the incidence of small cell carcinoma has also increased in recent years (12).

A relative decrease in the percent of central tumors compared to peripheral tumors has accompanied the change in histologic subtypes. Auerbach and Garfinkel (1) found a decrease in central tumors from 69.3 to 57.3 percent when comparing tumors seen prior to 1978 to those seen between 1986 and 1989.

The change in incidence in lung carcinoma subtypes may, in part, be related to changing histologic criteria in addition to a real change in incidence (4). Another complicating factor is the histologic heterogeneity of lung carcinomas, discussed in chapter 9.

Multiple separate primary carcinomas of the lung are well recognized; the incidence ranges from 0.2 to 2.0 percent of patients with lung carcinoma (2,9). Synchronous lung carcinomas are seen in about 2 percent of surgical resections (2). Of 50 cases reported by Martini and Melamed (8), 18 were synchronous and 32 were metachronous, with the time to diagnosis of the second tumor varying from 4 months to 16 years. The criteria for the diagnosis of two (or more) separate primary lung carcinomas used by Martini and Melamed are shown in Table 7-2. Squamous cell carcinoma is the most common subtype associated with multiple primary carcinomas of the lung, but many combinations occur (Table 7-3).

While gross and histologic features can be used to recognize synchronous primary lung carcinomas, other techniques may also be useful. Ichinose et al. (5) have shown that DNA flow cytometric patterns can separate synchronous primaries from intrapulmonary metastases.

Table 7-2

CRITERIA FOR DIAGNOSIS OF MULTIPLE PRIMARY LUNG CARCINOMAS*

Metachronous tumors
1. Histologically different**
2. Similar histology, but
   a. free interval between tumors of at least 2 years
   b. origin from carcinoma in situ
   c. second tumor in different lobe, but
      (1) no carcinoma in lymphatics common to both tumors
      (2) no extrapulmonary metastases at time of diagnosis

Synchronous tumors
1. Tumors physically distinct and separate
2. Histology
   a. different**
   b. same, but in different segments if
      (1) origin from carcinoma in situ
      (2) no carcinoma in lymphatics common to both
      (3) no extrapulmonary metastases at time of diagnosis

*Modified from reference 8.
**Adequate sampling mandatory.

Table 7-3

HISTOLOGY OF MULTIPLE PRIMARY LUNG CARCINOMAS*

Cell Type		Synchronous	Metachronous	Total
Tumor #1	Tumor #2			
Squamous	Squamous	31	59	90
Squamous	Adenocarcinoma	21	10	31
Squamous	Small cell	22	13	35
Squamous	Large cell**	5	6	11
Adenocarcinoma	Adenocarcinoma	4	9	13
Adenocarcinoma	Small cell	5	1	6
Adenocarcinoma	Large cell**	1	2	3
Small cell	Large cell**	1	0	1
Large cell**	Large cell**	4	1	5
		94	101	195

*Modified from reference 8 (195 cases).
**Includes some unspecified "anaplastic carcinomas."

INCIDENCE

Data from the American Cancer Society show that in 1989 carcinoma of the lung was the most common cause of cancer death in both men (34.1 percent) and women (19.9 percent) (14). It was estimated that 170,000 new cases of lung carcinoma would occur in the United States in 1993. Based on data from the United States for the year 1989, 23.1 percent of all deaths were due to cancer, and 27.6 percent of the cancer deaths were due to carcinoma of the lung. Thus, approximately 6.4 percent of all deaths in the United States in 1989 were due to carcinoma of the lung. The age-adjusted cancer death rate for 1989 was close to 30 per 100,000 for women and 75 per 100,000 for men.

Death rates from lung carcinoma have risen steadily in both men and women since 1930, with the rise occurring earlier and being steeper in men. However, since 1970 there has been a sharp increase in the death rate in women (14). Evidence suggests that the rate may be leveling off or decreasing in men as a result of public health efforts to curb cigarette smoking (15).

ETIOLOGY AND PATHOGENESIS

Cigarette smoking is the major cause of lung carcinoma in the United States and around the world (38). The lung carcinoma rate parallels smoking prevalence. There is a dose-response association between the number of cigarettes smoked and the risk of carcinoma of the lung, although changes in the composition of cigarettes and the introduction of filter tips in the 1950s and 1960s have lowered the risk of lung carcinoma 20 to 50 percent compared to earlier "high yield" cigarettes (30). The risk of lung carcinoma is also increased in individuals who are pipe or cigar smokers. The increased risk in smokers is seen for all types of lung carcinoma and decreases exponentially over time after cessation of cigarette smoking (38).

There are some variations in the histologic subtypes among smokers and nonsmokers (Table 7-4), with squamous cell carcinoma and small cell carcinoma showing the highest association with smoking. It is possible that the recent decrease in the frequency of squamous cell carcinoma is in part attributable to changing smoking habits (1).

Table 7-4

HISTOLOGIC SUBTYPES OF CARCINOMA IN SMOKERS AND NONSMOKERS*

Histologic Subtype	Smokers** (percent)	Non-smokers† (percent)
Squamous cell carcinoma	98.0	2.0
Adenocarcinoma	81.6	18.4
Bronchioloalveolar carcinoma	70.6	29.4
Small cell carcinoma	98.9	1.1
Large cell carcinoma	93.3	6.7

*Modified from reference 9.
**No. = 2708.
†No. = 218.

Some 80 percent of lung cancer deaths in men and 75 percent of lung cancer deaths in women can be attributed to cigarette smoking (38,45). In addition, it has been estimated that up to 25 percent of cases of carcinoma of the lung occurring in nonsmokers are the result of passive exposure to cigarette smoke (38), but this is controversial. In one study, 17 percent of the cases of lung carcinoma in nonsmokers were ascribed to childhood or adolescent exposure to cigarette smoke (31).

Asbestos is thought to be responsible for 4,000 to 6,000 deaths per year from carcinoma of the lung, less than 5 percent of all lung carcinoma deaths (38). A strong dose-response effect has been shown between asbestos exposure and the development of lung carcinoma; all histologic subtypes can be seen. There is a synergistic and multiplicative effect of smoking and asbestos exposure, with a 50-fold increased risk in the development of lung carcinoma (25). Although there is considerable debate, several studies suggest that the increased risk of lung carcinoma from asbestos exposure is only seen in those individuals with concomitant asbestosis (50).

Radiation is known to cause lung carcinoma (38). The association has been most extensively studied in uranium miners exposed to radon daughters. All types of lung carcinoma are seen, and a dose effect has been shown. An increased incidence of lung carcinoma has also been found in atom bomb survivors (35). Recently, considerable

Table 7-5

AGENTS OR EXPOSURES WITH PROVEN, PUTATIVE, OR POSSIBLE ASSOCIATION WITH LUNG CARCINOMA*

Ionizing radiation	Tobacco smoke
Asbestos	Shipyard workers
Chloromethyl ether	Truck drivers
Cadmium	Plumbers
Arsenic	Rubber workers
Chromate	Coke oven workers
Hexavalent chromium	Petroleum workers
Formaldehyde	Mustard gas workers
Terpenes	Coal tar workers
Vinyl chloride	Roofers
Soots and tars	Pottery workers
Nickel	Printers
Isopropyl oils	Female cosmetologists
Antimony	Leather industry workers
Beryllium	Building laborers
Cobalt	Construction workers
Iron and iron oxides	Cooks, bakers, and pastry cooks
N-nitrosamines	Asbestos insulation workers
Polycyclic aromatic hydrocarbons	Uranium miners
Fibrous zeolites	
Manmade mineral fibers	Other factors:
Fiberglass	Lung scarring
Glass wool	Alveolar epithelial hyperplasia/ bronchioloalveolar cell adenoma
Rock wool	Previous bronchogenic carcinoma
Ceramics	Hereditary carcinomas (chapter 3)
Alumina	
Lead	

*From references 17,25,28,35,38,39,42,43.

interest has centered on nonoccupational exposure to radon daughters in houses. Some studies have suggested that 5 to 15 percent of lung carcinomas are due to nonoccupational radon daughter exposure and that these cases account for 25 percent of the lung carcinomas occurring in nonsmokers and for 5 percent of the carcinomas in smokers (38). These figures have not been universally accepted (21), and further confirmatory studies are needed.

There has been some evidence that diet may have an impact on the risk of carcinoma of the lung. In a review by Colditz et al. (26), it was concluded that vitamin C might offer slight protection from lung carcinoma, but there was little evidence that vitamin C or vitamin E had any major influence. Data on a protective effect from selenium was limited but thought to warrant further study.

There are a number of other potential or proven agents or exposures associated with an increased risk of lung carcinoma, as shown in Table 7-5. In some instances, an occupation is associated with an increased incidence of carcinoma of the lung, but the specific causative agent or agents have not been identified. Some of the exposures listed in Table 7-5 are controversial and not universally accepted as proven or putative causes of lung carcinoma.

The concept of *scar carcinoma*, namely carcinoma of the lung arising in the vicinity of fibrosis (fig. 7-2), has been accepted for decades since first being studied in 1930s (17,36). In early studies, most of the scars were attributed to old tuberculosis; however, infarcts, pneumoconioses, and other chronic inflammatory scarring of the lung have all been implicated in individual

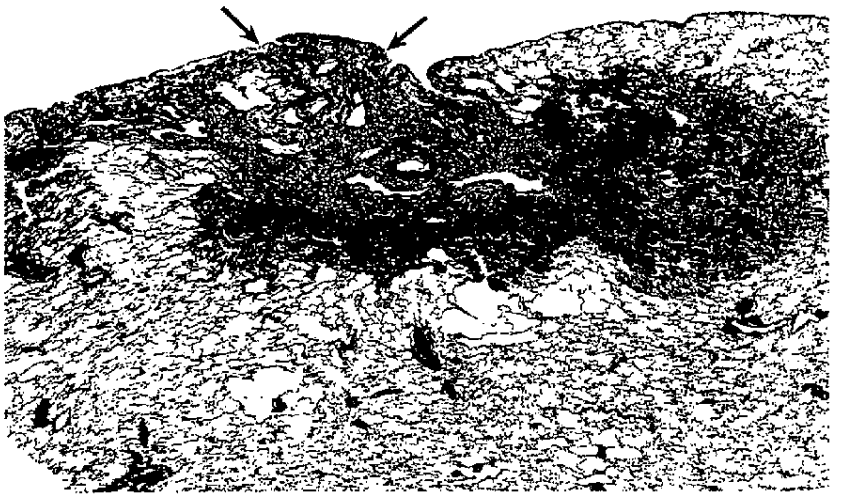


Figure 7-2
SCAR CANCER

Small peripheral adenocarcinoma, bronchioloalveolar type, arising in association with a scar. There is a scar associated with some pleural puckering (arrows) around and from which the darker-appearing neoplasm extends. The surrounding lung tissue shows no significant fibrosis and only slight emphysema. In the majority of such cases, including this, the scar is probably the result of, rather than a precursor to, the carcinoma.

cases. In some studies, nearly half of all peripheral lung carcinomas were associated with a scar (36). The concept of scar carcinoma suggests that progressively atypical epithelial changes develop in the vicinity of the scar and ultimately lead to the development of a carcinoma. Meyer and Liebow (36) and subsequently others (27,51) described lung carcinomas arising in association with diffuse interstitial fibrosis and drew an analogy with carcinomas associated with focal scarring.

Tumors that have been labeled scar carcinomas are typically subpleural adenocarcinomas associated with retraction or puckering of the overlying pleura (17,22). Cut sections grossly show a central sclerotic zone ("scar") which may have anthracotic pigment and necrosis. Larger tumors (greater than 3 cm) tend to have more extensive scarring (22). In 1980, Shimosato (49) and subsequently others (22,32–34) suggested that the fibrosis in most scar carcinomas is a secondary phenomenon rather than a precursor to the carcinoma. Studies showed that the scar had abundant type III collagen and an extracellular matrix, suggesting an ongoing fibrosing process supporting a host response to the neoplasm (19,34), i.e., these tumors were desmoplastic carcinomas rather than carcinomas arising in scars.

Nevertheless, there are well-documented cases (52) showing carcinomas arising adjacent to old granulomas (fig. 7-3). It seems likely, however, that most scars are a secondary reaction rather than a preexisting lesion. This phenomenon is easily appreciated in sclerosing bronchioloalveolar carcinomas (chapter 13) in which only the alveolar walls involved by carcinoma are inflamed, thickened, and fibrosed.

While the pathogenesis of many scar carcinomas has been questioned, the concept of *atypical type 2 cell hyperplasia* (*atypical adenomatous hyperplasia*) as a precursor of adenocarcinoma has been reemphasized in several recent studies (23,40,41). Nakanishi (40) studied 15 cases of alveolar epithelial hyperplasia coexistent with lung carcinoma in a series of 70 patients. A histogenetic relationship between atypical alveolar epithelial hyperplasia (fig. 7-4) and pulmonary adenocarcinoma was suggested. Nakayama et al. (41) showed that atypical adenomatous hyperplasia (probably synonymous with *atypical alveolar epithelial hyperplasia*) was a clonal cellular proliferation closely related to well-differentiated adenocarcinoma.

In a series of 247 consecutive resections for carcinoma of the lung, Miller (37) found 23 (9.3

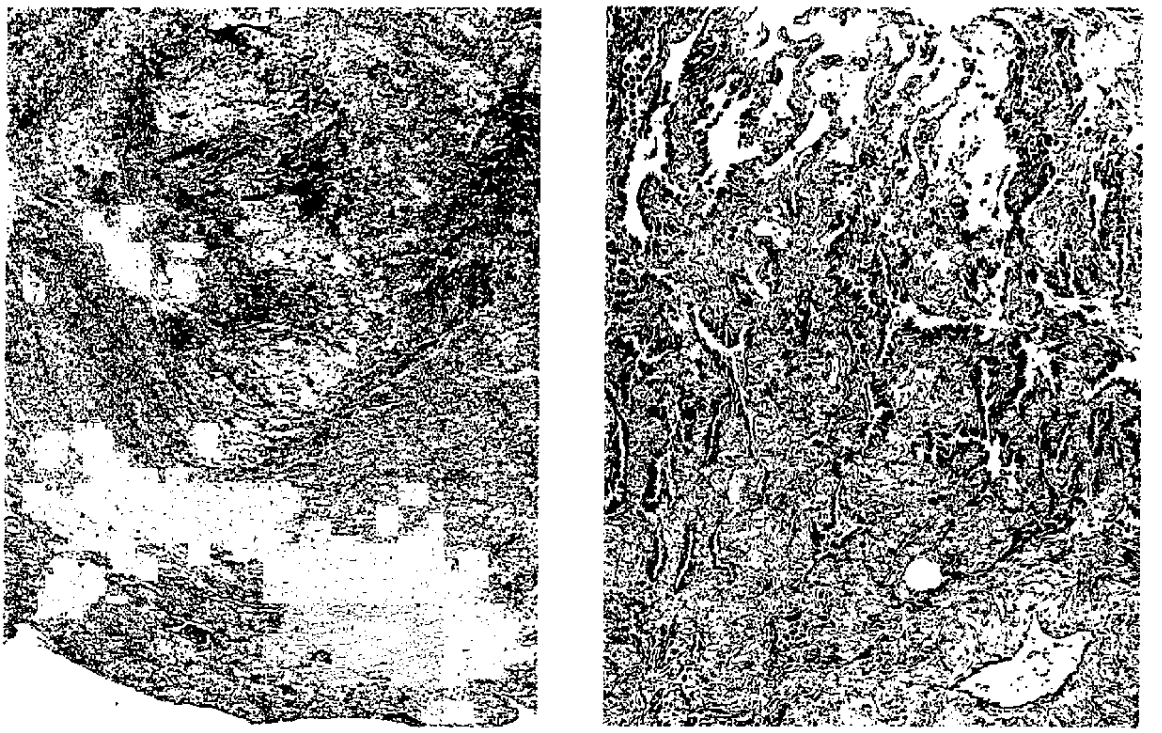


Figure 7-3
SCAR CANCER

Adenocarcinoma arising in association with a scar. These sections are from a physician's wife who had been followed for several decades with a stable lesion on her chest radiograph following a documented bout of tuberculosis. When the radiographic lesion started to enlarge, it was resected. Evidence of old healed granulomatous disease with increased anthracotic pigmentation can be seen at the left; in the surrounding fibrotic tissue, there is a proliferation of atypical epithelium (lower left and right) which was continuous with an obvious bronchioloalveolar carcinoma extending from the edge of the fibrotic region. This case probably represents a bona fide scar carcinoma.

percent) with incidental 1- to 7-mm nodules separate from the main tumor mass. These nodules were composed of localized proliferations of type 2 cells and were termed *bronchioloalveolar cell adenomas* (chapter 13). Miller concluded that these adenomas might be an early or premalignant phase of glandular neoplasia with the potential for progression to carcinoma. She also suggested that the finding might explain some examples of multicentricity among lung carcinomas. In individual cases, atypical type 2 cell hyperplasia and bronchioloalveolar cell adenoma may be difficult to distinguish and part of a disease spectrum.

Patients with a history of a resected lung carcinoma have an appreciable risk of a second lung carcinoma. The risk is in the range of 2 percent per year for patients with long-term survival (over 5 years) (44). Long-term survivors of small cell carcinoma have a particularly high risk, estimated at 5.6 percent per person year (29).

Bejui-Thivolet et al. (20) have used in situ hybridization to show the presence of human papilloma virus (HPV) DNA in well-differentiated squamous cell carcinomas of the lung. They studied 33 carcinomas and 10 bronchial squamous metaplasias with probes for HPV subtypes 6, 11, 16, and 18. Of the 43 cases studied, 7 showed the presence of HPV DNA, including 1 case of squamous cell metaplasia and 6 cases of squamous cell carcinoma. Fourteen of the 43 lesions studied showed condylomatous changes, and 6 of the 7 cases in which HPV was detected by in situ hybridization came from among these cases. The authors suggested that HPV infection might be potentially oncogenic in the lung as it

Figure 7-4
ATYPICAL ADENOMATOUS HYPERPLASIA

There is a relatively uniform proliferation of low cuboidal cells lining alveolar walls. Obvious cytologic features of malignancy are not present. Such atypical adenomatous hyperplasia is thought by some to represent a precursor to the development of adenocarcinoma of the lung, and such proliferations are relatively common in lungs resected for bronchioloalveolar carcinoma, as was this case.

is in the genital tract, but that its exact role needs to be clarified.

The morphogenesis of squamous cell carcinoma has been studied for several decades and is illustrated cytologically in figures 7-5 and 7-6. Since cigarette smoking increases squamous metaplasia (46), most studies have used serial sputum cytology specimens from cigarette smokers (16,18) or uranium miners. There is loss of normal ciliated lining cells with basal cell hyperplasia, low columnar nonciliated epithelium or squamous metaplasia, and increasing degrees of atypical squamous metaplasia (dysplasia), ultimately followed by squamous cell carcinoma in situ (CIS) and invasive squamous carcinoma. Not all cases of CIS of the bronchial tree are progressive, and some cases regress (24).

In practice, CIS is not found in all patients with squamous cell carcinoma and rarely in other histologic subtypes of lung carcinoma. In meticulous studies of serial sections of the bronchial tree taken at autopsy, Auerbach (18) found CIS in 26 of 34 patients with carcinoma of the lung. It is much less frequently seen in surgical specimens, as shown in the data of Rilke et al. (47): CIS at the bronchial margin was seen in only 3 of 67 cases (4.5 percent).

The molecular biology of carcinogenesis in the lung is discussed in chapter 3.

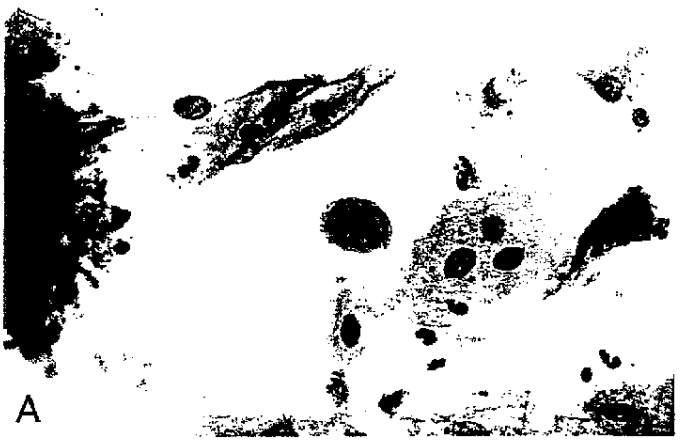
SCREENING FOR CARCINOMA OF THE LUNG

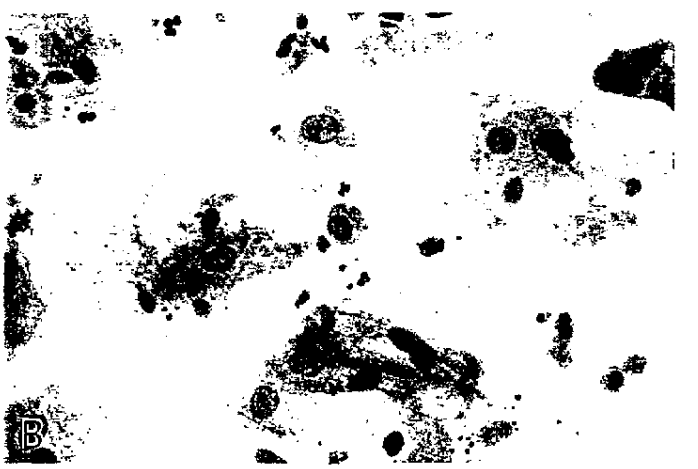
In 1971, the National Cancer Institute organized the Cooperative Early Lung Cancer Group to develop a screening program for the early detection of lung cancer in high-risk patients (male smokers) (53–59). Over 30,000 men older than 45 years of age enrolled in the study; at the time of entry into the study, none were suspected of having a lung carcinoma. Sputum cytologic examinations, chest radiographic examination, or both, along with a medical questionnaire were the screening tests used.

At the initial screening, a number of unsuspected lung carcinomas were identified, and these comprised the prevalence cancers in the study. The proportion of cases in each histologic subtype was roughly similar to that for all cases of lung carcinoma. Fifty-nine percent of the tumors were resectable, a figure more than double that seen in routine practice.

The carcinomas that were detected during the study period represented the incidence cancers. A number of both the prevalence cancers and the incidence cancers represented early or occult lung carcinomas, which are described and illustrated in chapter 10.

The study showed that with screening there was increased cancer detection, resectability, and survival. Regarding the incidence cancers: less than half were actually detected by the screening studies despite rescreening every 4 months; cancers detected on the basis of clinical symptoms were rarely resectable; and the proportion that could be completely resected was 46 percent for the screened group and 32 percent for the control group (58).





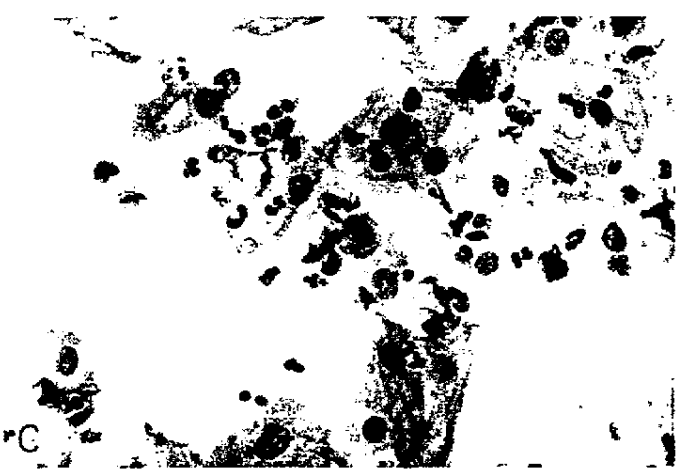
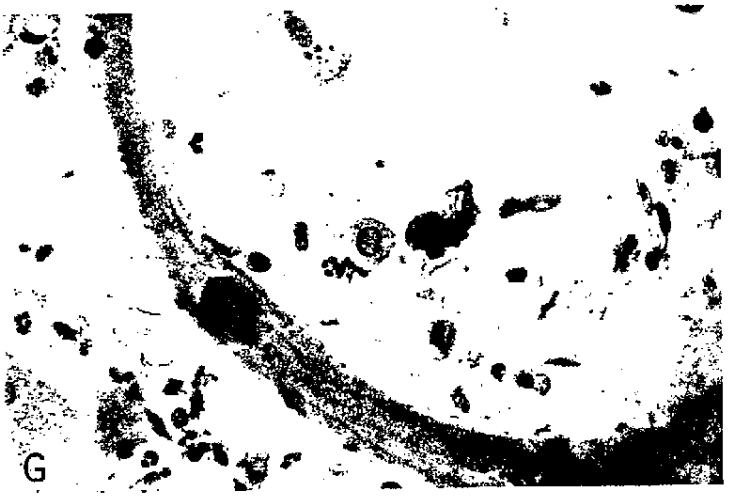


Figure 7-5

MORPHOGENESIS OF CARCINOMA OF THE LUNG .

Mild (A–C), moderate (D–F), and severe (G–I) squamous atypia (dysplasia) developing in uranium miners followed with sputum cytology examinations. (Courtesy of Drs. G. Saccomanno and M. Turner, Grand Junction, CO.)

Figure 7-5 (Continued)



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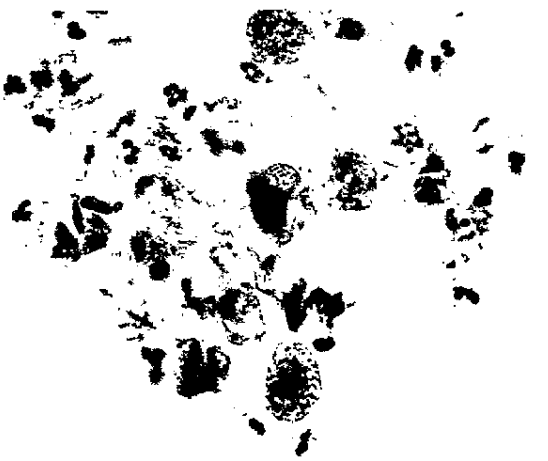

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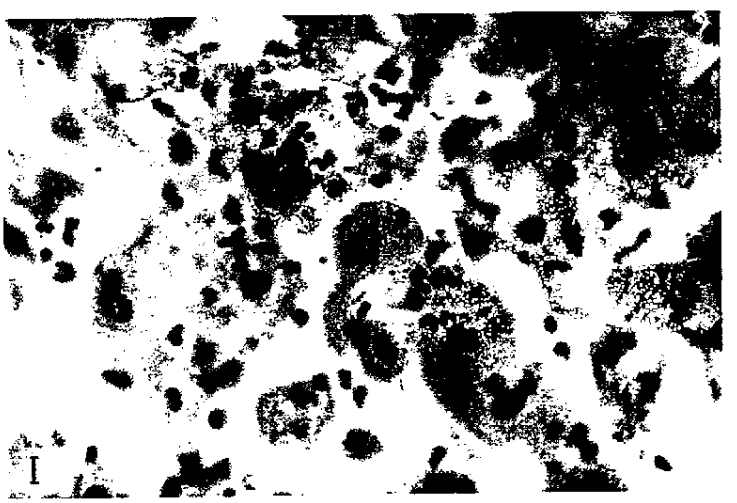

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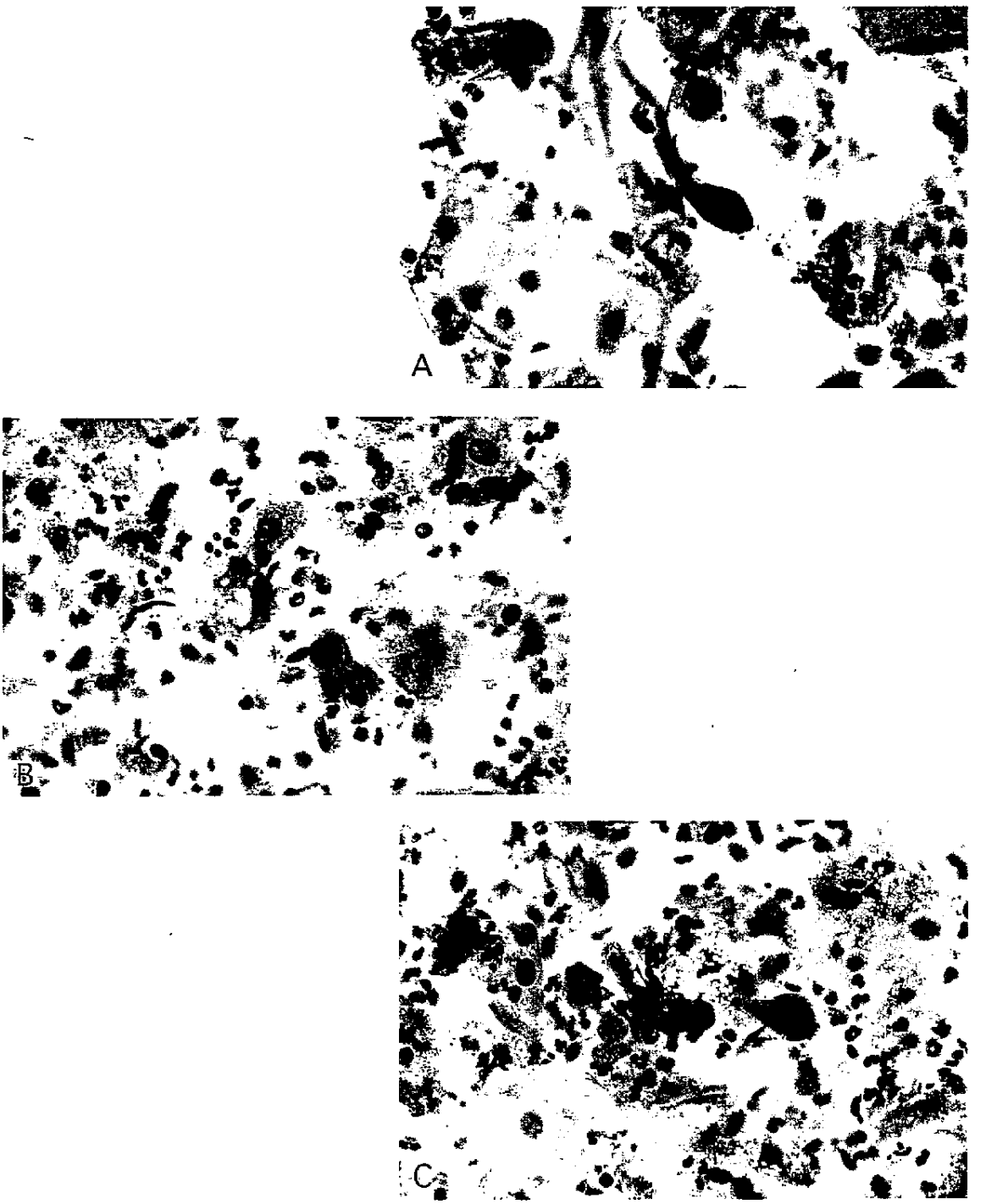
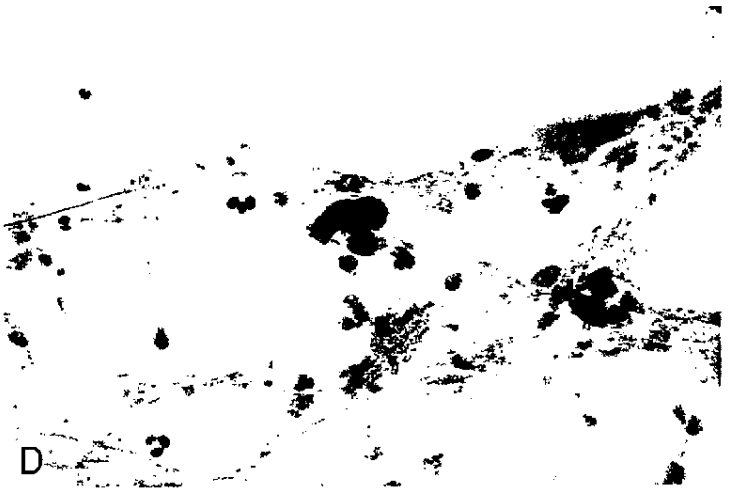
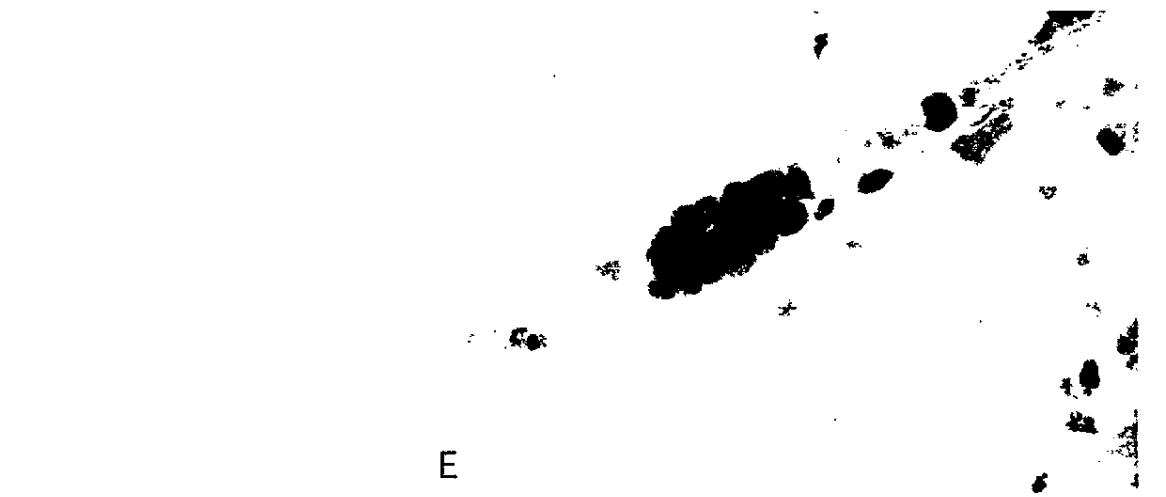


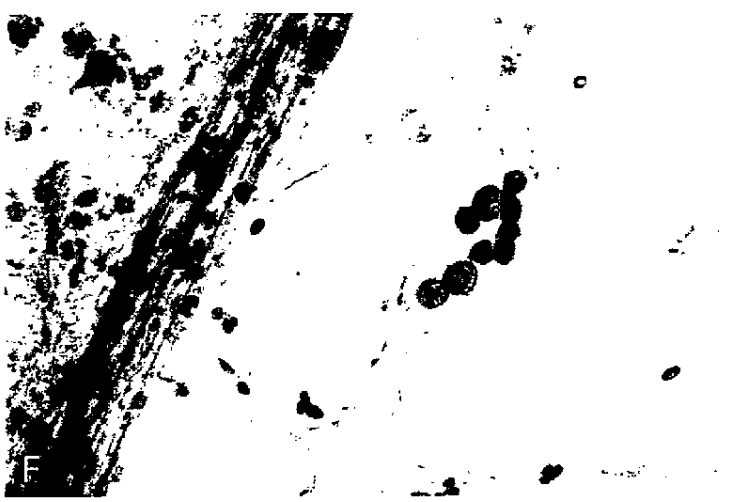
Figure 7-6

MORPHOGENESIS OF BRONCHOGENIC CARCINOMA

Even though degrees of squamous atypia (dysplasia) may progress to squamous cell carcinoma (A–C), squamous atypia may also precede small cell carcinoma (D–F) or adenocarcinoma (G–I) in uranium miners. (Courtesy of Drs. G. Saccomanno and M. Turner, Grand Junction, CO.)







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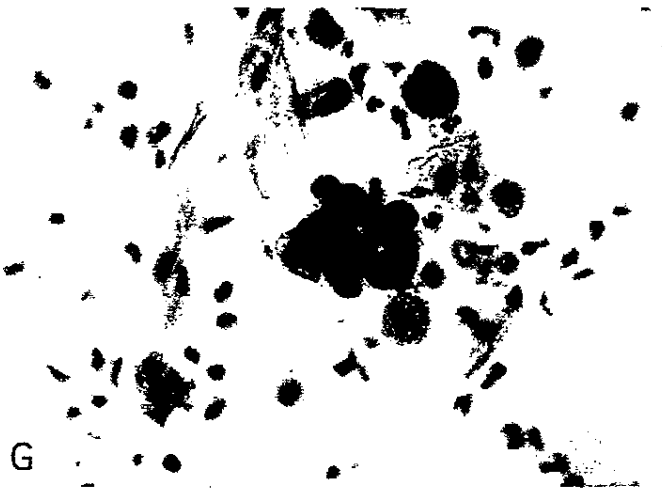

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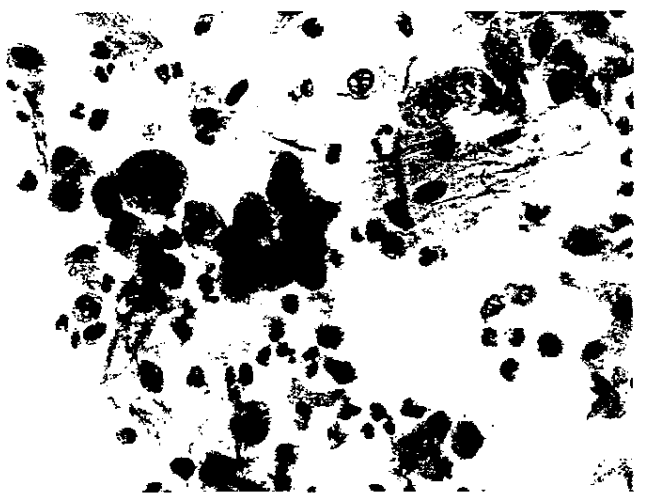

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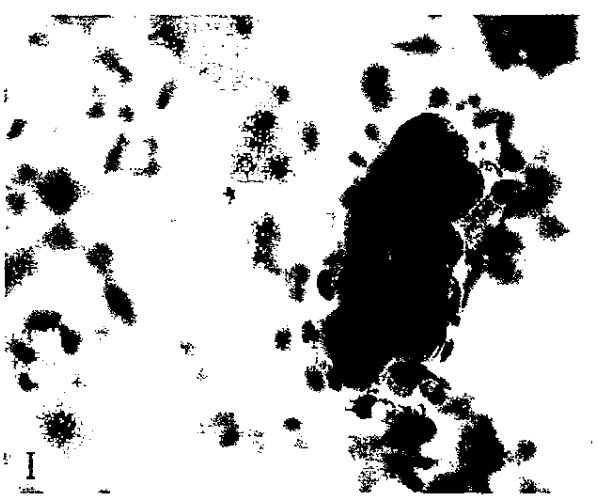

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Figure 7-6 (Continued

Table 7-6

DETECTION OF LUNG CARCINOMA BY SCREENING METHODS*

	% Detected By:		
	X Ray Only	Cytology Only	X Ray & Cytology
Squamous cell (no. = 81)	38	43	19
Adenocarcinoma (no. = 43)	81	0	19
Small cell (no. = 15)	73	0	27
Large cell (no. = 20)	75	10	15

*From reference 54.

The screening methods showed considerable variability in effectiveness for identifying histologic subtypes of lung carcinoma (Table 7-6). Over 60 percent of the squamous cell carcinomas had a positive cytology, and in data not shown, it was found that 95 percent of all cancers detected by cytology alone were squamous cell carcinomas (54). For the other histologic subtypes, the chest radiograph was the primary means of detection.

The 5-year survival data from the Mayo Lung Project revealed the following (56): cases identified cytologically, about 80 percent; cases identified roentgenographically, about 35 percent; symptomatic cases, about 10 percent; every 4-month screened group, about 35 percent; and control group, less than 15 percent.

Despite these findings, there was no statistically significant difference in the mortality rate for lung carcinoma between the study groups and the control groups, either in the Mayo Lung Project or in the other two institutions taking part in the study (56). For the Mayo Lung Project there were 122 lung cancer deaths in the study group (3.2 per 1000 man years) and 115 lung cancer deaths in the control group (3.0 per 1000 man years). Although tumors were detected in the study group and overall there was a better 5-year survival, the fact that the mortality rates were similar between the study group and the control group suggests that some of the tumors identified in the study group may have been relatively indolent and slower growing and might not have manifested for a number of years or been fatal. It is possible that these tumors had inherent biologic differences from the more highly aggressive tumors that accounted for the mortality in both groups and characterize most lung carcinomas.

Other general conclusions from the Cooperative Early Lung Cancer Group study were (54): 1) the chest roentgenogram is the most sensitive method available for detecting lung carcinoma, and 2) sputum cytology is the most effective method for detecting early squamous cell carcinoma of the lung.

These studies suggest that mass screening does not have a significant impact on mortality, and thus question the usefulness of mass screening for carcinoma of the lung. This conclusion has recently been challenged by Strauss et al. (61) who concluded, after reworking the original data, that there was insufficient evidence to firmly recommend against lung cancer screening.

While mass screening may not have a significant impact on mortality, screening of select populations may yet prove to be of value. Saccomanno et al. (60) described the results of periodic cytologic examinations of sputum in a group of uranium miners, a subset now known to be at high risk for the development of lung carcinoma. In this group, abnormalities progressed in degree over time and changes were readily detectable in sputum cytology specimens (figs. 7-5, 7-6); there was an average of 4 to 5 years during which individuals would exfoliate abnormal cells prior to the development of an invasive carcinoma. The authors concluded that this 4- to 5-year period represented a window of opportunity for early detection and treatment.

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